Cardiac CARE

Statistical Analysis Plan

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Document Control		
Version No	**Date**	**Summary of Revisions**
1.0	30May2022	Creation of new SAP
2.0	30Jun2022	Minor updates to the SAP to clarify that age has to be calculated from consent instead of randomisation, as it was discovered in preprograming that age of randomisation is not feasible for all patients and further specification of baseline points for several endpoints.

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List of Abbreviations

Abbreviation	Full name
ARB	Angiotensin Receptor Blocker
BP	Blood Pressure
bpm	Beats per minute
CM	Centimetre
CONSORT	Consolidated Standards of Reporting Trials
CRIC	Clinical Research Imaging Centre (at the University of Edinburgh)
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
cTnI	Cardiac troponin I
ECTU	Edinburgh Clinical Trials Unit
eGFR	estimated Glomerular Filtration Rate
fMRI	functional Magnetic Resonance Imaging
GCS	Global Circumferential Strain
GLS	Global Longitudinal Strain
Hs-cTnI	High sensitivity cardiac troponin I
IMP	Investigational Medicinal Product
ITT	Intention to treat
Kg	Kilogramme
L	Litre
LAA	Left Atrial Area
LVEF	Left ventricular ejection fraction
LVM	Left Ventricular Mass
LVV	Left Ventricular Volume
M	Metre
Mg	Milligram
mmol	Millimole
MRI	Magnetic Resonance Imaging
N	Number of patients with an observation
ng	Nanogram
QC	Quality Control
SAP	Statistical analysis plan
SAS	Statistical Analysis Software (a proprietary analysis package) [1]
SD	Standard Deviation
SOP	Standard operating procedure
TOST	Two One Sided Tests
Y/N	Yes/No

1. Introduction

This document details the criteria to be used for the definition of the analysis populations and the statistical methodology for analysis for the Cardiac CARE trial, a randomised trial of candesartan, carvedilol plus standard care, versus standard care alone, to prevent cardiac toxicity in breast cancer and lymphoma patients receiving anthracycline adjuvant therapy. This document has been compiled according to the Edinburgh Clinical Trials Unit (ECTU) standard operating procedure (SOP) "Statistical Analysis Plans" ECTU_SOP_ST_04 version 6.0 and has been written based on information contained in the study protocol version 11.0, dated 27 July 2021.

Cardiac Care is a multi-centre, randomised, open-label parallel-group trial. Patients are enrolled in the study, and started on anthracycline adjuvant therapy. They are randomised at the point that they exhibit suitably elevated cTnI concentrations, with patients that do not exhibit such levels being retained in a non-randomised (low-risk) group. Thus, there are 3 intervention groups being studied: non-randomised (low-risk); randomised to candesartan, carvedilol and standard care; randomised to standard care alone. Randomisation is at the individual level with a 1:1 allocation ratio, with minimisation by age, baseline LVEF, and planned cumulative epirubicin equivalent dose. The aim is to randomise 56 patients.

2. Statistical Methods section from the protocol

ECTU statisticians will be responsible for analysis of the study data. The Data Analysis will be conducted independently of data entry.

The MRI Imaging from all the sites will be transferred to CRIC for detailed MRI analysis by two cardiac MRI analysts. The image analysts at CRIC will be blinded to treatment allocation and are not involved with scanning or contact with patients. CRIC will provide these data for the study database. ECTU statisticians will not be responsible for analysis of MRI data.

The primary analysis will be change in LVEF on cardiac MRI 6 months following completion of anthracycline between randomized treatment groups, using linear regression, adjusted for age, baseline LVEF and baseline planned cumulative epirubicin equivalent dose. This will be an intention-to-treat, and treatment effect will be expressed by a point estimate and its 95% confidence interval. We will keep missing values to a minimum, and the primary analysis will be a complete case analysis. If there are sufficient missing data to cause concern, multiple imputation will be used as a sensitivity analysis.

The specificity of the cTnI assay for left ventricular dysfunction in non-randomised participants will be assessed by calculating the mean of the within-person changes between participants' pre and post-anthracycline MRI scans, plus its 95% confidence interval. This confidence interval will be compared to the equivalence limits of ±2%. Specificity will be evaluated by the data monitoring committee who will advise whether conducting post-anthracycline cardiac MRI scans on remaining non-randomised participants in the study will be necessary.

Other secondary outcomes will be analysed appropriately – linear regression for continuous outcomes, logistic regression for binary outcomes, and Cox proportional hazards for survival analysis, adjusted as for the primary analysis. A full Statistical Analysis Plan will be finalized before database lock.

3. Description of analysis datasets

The analysis datasets are detailed below. All analyses will be performed on the intention to treat population unless otherwise specified.

Note: One participant recorded a high troponin value at cycle 6 and that should have triggered a randomisation. However, they were not randomised because they had already been started on candesartan (an ARB) for non-trial, clinical reasons (prior to the troponin threshold being reached). The clinicians discussed this and agreed that randomisation should not take place because the patient was already receiving candesartan, and that this is not a violation because it was done to protect patient safety. The sponsor agreed this is not a violation because the participant was not eligible for randomisation (taking ARB is an exclusion criterion). The patient was entered into the study database, non-randomised and taking candesartan, but not as an IMP. This information should be in the Concomitant Medication section of the database and can be picked up from there. The participant would not appear in the intention to treat population, as they were never randomised. He/she will need to be removed from other populations, as he/she is not representative of non-treated patients as his/her troponin value would have triggered randomisation and he/she received the IMP. This will need to be described appropriately in e.g. a footnote to the CONSORT flow chart, to ensure it is clear what happened.

All recruited patients: The All recruited patients population will include all patients who have been recruited into the Cardiac CARE trial, and who did not withdraw consent for their data to be stored in the trial database, according to the Change of Status form*. Patients who, during the Cardiac CARE study, were started on candesartan outside of the randomised trial, will be removed. If tables require, these data will be split into randomised/non-randomised. If required, the randomised data can be split by allocated intervention, with participants analysed in the group to which they were allocated, regardless of the intervention they actually received.

Intention to treat: The intention-to-treat (ITT) population will include all patients who have been randomised into the Cardiac CARE trial, and who did not withdraw consent for their data to be stored in the trial database, according to the Change of Status form*. Patients will be analysed in the intervention group to which they were allocated, regardless of the intervention they actually received.

Safety: The safety population will include all patients who have been randomised into the Cardiac CARE trial, and who did not withdraw consent for their data to be stored in the trial database, according to the Change of Status form*, patients will be analysed by the intervention they received.

*The Change of Status that denotes participants should be removed from the trial database is ‘c. Not for use’.

4. Overall Statistical Principles

In general terms, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, median, standard deviation (SD), minimum, maximum, lower and upper quartiles and number of patients with an observation (N). Data will be split by intervention group and time point where applicable.

All applicable statistical tests for a difference will be 2-sided and will be performed using a 5% significance level. 95% (2-sided) confidence intervals will be presented. All analyses are testing superiority, rather than equivalence or non-inferiority, unless otherwise specified. There will be no adjustment for multiplicity of outcome measures.

Where there is missing data for an outcome variable, in the first instance, those records will be removed from any formal statistical analysis relating to that outcome variable (complete case analysis), unless otherwise specified. In tabulations, numbers of missing observations will be provided, but percentages will not include them.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots. If the distributional assumptions for the parametric approach are not satisfied, further data transformation (to alleviate substantial skewness (i.e. normalizing) or to stabilise the variance), or other suitable methods will be considered. This will be documented in the statistical results report together with the reasoning supporting the action taken, if applicable. If final analyses do not follow this SAP for any reason, an updated SAP will be written together with the reasoning for the action taken. This will also be documented in the statistical report.

The main statistical analyses for primary and secondary outcomes will be adjusted for the minimisation variables: age at consent, baseline LVEF, and planned cumulative epirubicin equivalent dose, unless doing so causes problems due to collinearity. These will be adjusted for as binary fixed effects: age ≥65 or <65 years; baseline LVEF ≥60% or <60%; planned cumulative epirubicin equivalent dose 300 mg/m^2 or >300 mg/m^2. Baseline LVEF will be the finalised core lab value.

All analyses will be carried out using the most up to date version of SAS available [1].

NB. There are multiple values recorded for LVEF in the database due to the adjudication system. The statistical analysis will use the finalised core lab values [variable name = RepeatLVEF]. This only affects LVEF and not global longitudinal strain, global circumferential strain, left ventricular volume, left atrial area, left ventricular mass.

5. List of Analyses

Health economic and fMRI analyses will be performed by the health economics team and the imaging team at CRIC respectively, and are not described in this SAP.

5.1 Study populations, recruitment and retention

Note: Unless otherwise specified, no formal statistical testing will be performed and data summaries and analyses will be presented overall and by the intervention group.

The following dates will be reported: date first patient consented, date last patient consented and entered into study, date first patient recruited, date first patient randomised, date last patient randomised. [Population = All recruited patients]

The following will be tabulated: The total number of patients consented; with this number split into the number of patients not randomised and randomised; with those randomised split by allocated intervention. The number of centres that randomised patients, with the number of patients randomised by each centre. [Population = All recruited patients]

Graph: Cumulative number consented over time, and randomised over time (both lines on the same graph). [Population = All recruited patients]

A CONSORT flow chart will be constructed jointly by the Cardiac Care Trial Manager and statistician – the Trial Manager will provide information prior to consent, and the statistician will provide information after that point. Reasons for non-inclusion in the study (prior to randomisation) will be categorised. The number of patients discontinued early from the study will be summarised by reason for withdrawal and intervention group.

The following will be presented:

- Number of patients who randomised but were ineligible for inclusion in trial (if any – it should not have been possible to randomise such patients). If there were none, then a statement will be added to the statistical report.
- Numbers of patients who were randomised but never treated (if any).
- Numbers of patients who received the opposite intervention to that allocated (if any)

Tabulation: Treatment cycle at which participants were randomised. [Population = All recruited patients]

Tabulation: Numbers of patients in the all recruited patients, intention to treat and safety populations.

Tabulation: Person-years of follow-up for patients included in analysis of primary outcome (measured at 6 months) by allocated intervention, with proportion of this time that was after the start of the COVID-19 pandemic [16 March 2020].

5.2 Baseline characteristics

Population = All recruited patients.

The following baseline characteristics are to be tabulated by the 3 intervention groups (active, control, non-randomised), for the combined randomised groups (active and control), and for the entire recruited group. No formal statistical testing of the baseline characteristics will be performed.

Patient demographics: Age at consent (years) [continuous, and as <65 or ≥65], sex [binary], height (cm) [continuous], weight (kg) [continuous], pregnancy test done [Y/N], reason for not doing pregnancy test [categorical], smoking status [categorical].

Relevant medical history: history of diabetes [categorical], history of coronary artery disease [Y/N], history of hypertension [Y/N], history of heart failure [Y/N], history of kidney disease [Y/N].

Primary presenting complaint: cancer disease type [categorical], planned epirubicin equivalent dose [continuous, and as 300 vs >300], planned number of anthracycline cycles [numerical categories]

Clinical observations at baseline: LVEF (%) [continuous, and as <60 or ≥60], Cardiac MRI - global longitudinal (GLS) and circumferential (GCS) myocardial strain, left ventricular mass (LVM), left ventricular volume (LVV) and left atrial area (LAA) at the cardiac MRI screening visit. Systolic blood pressure (mmHg) [continuous], diastolic blood pressure (mmHg) [continuous], pulse (bpm) [continuous] and Hs-cTnI concentration at cycle 1.

Concomitant medications: Medication categories with N patients and % - anti-infectives, cardiovascular agents, central nervous system agents, coagulation modifiers, gastrointestinal agents, genitourinary tract agents, hormones, immunologic agents, metabolic agents, psychotherapeutic agents, respiratory agents, topical agents, other.

Other relevant information: Co-enrolled into another CTIMP [Y/N]

5.3 Trial intervention details, and adherence

Population = Intention-to-treat. No formal statistical testing will be performed.
Detailed diary information has not been entered into the database, and is poorly completed. We will describe the adherence level to trial intervention using the titration visit form and dose change form. We will indicate the number of patients who never started, who started but stopped early, and who started and we have no indication that drug was stopped early (separating information where possible by candesartan and carvedilol). Where:

Early cessation = stopping both medications within 2 months of randomisation.
Partial cessation =stopping 1 medication (either candesartan or carvedilol) within 2 months, reporting which medication was stopped.
NOTE: Partial Interruptions in the IMPs (i.e. medication was eventually restarted), should not be included.

5.4 Outcomes

5.4.1 Primary outcome - Cardiac MRI – Change in LVEF

The primary outcome is the change in LVEF on cardiac MRI scan conducted 6 months after final anthracycline dose compared to baseline cardiac MRI scan conducted before anthracycline therapy starts.

***5.4.1.1 Descriptive statistics* LVEF**

Population = All recruited patients .

We will tabulate baseline LVEF (%) [continuous], 6 month LVEF (%) [continuous], within-person change in LVEF (%) [continuous].

***5.4.1.2 Efficacy analysis - Primary analysis of primary outcome* LVEF**

Using the ITT population, if relevant distributional assumptions hold, then the relationship between the allocated intervention and the primary outcome will be analysed using linear regression. The results will be expressed as the difference in means with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

We do not envisage that there will be sufficient missing data to cause concern (>10%), and multiple imputation is unlikely to be necessary.

There are no pre-planned subgroup analyses.

***5.4.1.3. Anthracycline cardiotoxicity and* LVEF**

Population = All recruited patients, but there will be no formal statistical testing.

1. A fall in LVEF of 10% points AND a fall in ejection fraction (LVEF) below 50%

2. Any fall in LVEF below 50%

3. Any fall in LVEF below 40%

We will tabulate the number of patients with and without the above outcomes, split by randomised/not randomised, and split by allocated intervention within the randomised group.

5.4.1.4. Specificity of hs-cTnI assay for cardiotoxicity on* LVEF *– main secondary objective

Population = All recruited patients.

Analysis within the non-randomised group only. Post treatment LVEF will be recorded with cardiac MRI in all non-randomised participants and compared to baseline LVEF to define the specificity of the hs-cTnI assay for identifying low-risk participants who do not develop left ventricular systolic dysfunction. The aim is to demonstrate zero LVEF% change within the low risk non-randomised group with equivalence limits of ±2%. The specificity of the cTnI assay for left ventricular dysfunction in non-randomised participants will be assessed by calculating the mean of the within-person changes in LVEF between participants' pre and post-anthracycline MRI scans, plus its 95% confidence interval. This confidence interval will be compared to the equivalence limits of ±2%, using a Two One-Sided Tests (TOST) approach.

***5.4.1.5. Exploratory comparison of high-risk to low-risk patients for* LVEF**
Population = All recruited patients.

As an exploratory comparison for LVEF, we will present the mean of the within-person changes between participants' pre and post-anthracycline MRI scans, plus its 95% confidence interval, for the (high risk) group randomised to standard care, and for the (low risk) non-randomised group. We will calculate p-values using linear regression, adjusting as specified in the Overall Statistical Principles.

5.4.2 Cardiac MRI - global longitudinal (GLS) and circumferential (GCS) myocardial strain
5.4.2.1 Descriptive statistics
Population = All recruited patients.

We will tabulate baseline values [continuous], 6 month [continuous], within-person change [continuous]. We will present data split by non-randomised/randomised, and by allocated intervention within the randomised group.

5.4.2.2. Efficacy analysis - GLS / GCS
Population = Intention-to-treat.

Analysis of change in GLS and change in GCS. Using the ITT population, if relevant distributional assumptions hold, then the relationship between the allocated intervention and each outcome will be analysed using linear regression. The results will be expressed as the difference in means with the corresponding 95% confidence intervals and p-value. The analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

5.4.2.3. Anthracycline cardiotoxicity and GLS / GCS
Population = All recruited patients, but there will be no formal statistical testing.

A > 15 % (relative) fall in GLS or GCS on 6 month post-anthracycline cMRI. This will be calculated as [(6 month value – baseline value)/Baseline value]*100. So a 'reduction' from -18.0% to - 15.2% would be a >15 % change.

We will tabulate the number of patients with and without the above outcome, split by non-randomised/ randomised, and by allocated intervention within the randomised group.

5.4.2.4. Specificity of hs-cTnI assay for cardiotoxicity on GLS / GCS
Population = All-recruited patients.

Analysis within the non-randomised group only. Post treatment GLS and GCS will be recorded with cardiac MRI in all non-randomised participants and compared to baseline GLS and GCS to define the specificity of the hs-cTnI assay for identifying low-risk participants who do not develop left ventricular systolic dysfunction. The aim is to demonstrate zero GLS and GCS change within the low risk non-randomised group. The specificity of the cTnI assay for left ventricular dysfunction in non-randomised participants will be assessed by calculating the mean of the within-person changes in GLS and GCS between participants' pre and post-anthracycline MRI scans, plus its 95% confidence interval. There will be no formal testing of equivalence.

5.4.2.5. Exploratory comparison of high-risk to low-risk patients for GLS / GCS
Population = All recruited patients.

As an exploratory comparison, we will present the mean of the within-person changes between participants' pre and post-treatment GLS and GCS values, plus their 95% confidence intervals, for the

(high risk) group randomised to standard care, and for the (low risk) non-randomised group. We will calculate p-values using linear regression, adjusting as specified in Overall Statistical Principles.

5.4.3 Cardiac MRI - left ventricular mass (LVM), left ventricular volume (LVV) and left atrial area (LAA)

5.4.3.1 Descriptive statistics

Population = All recruited patients.

We will tabulate baseline values [continuous], 6 month [continuous], within-person change [continuous]. This will be split by non-randomised/randomised, and by allocated intervention within the randomised group.

5.4.3.2. Efficacy analysis – LVM/LVV/LAA

Population = Intention-to-treat.

Analysis of change in left ventricular mass, left ventricular volume and left atrial area. Using the ITT population, if relevant distributional assumptions hold, then the relationship between the allocated intervention and each outcome will be analysed using linear regression. The results will be expressed as the difference in means with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

5.4.3.3. Specificity of hs-cTnI assay for cardiotoxicity on LVM/LVV/LAA

Population = All-recruited patients.

Analysis within the non-randomised group only. Post treatment left ventricular mass, left ventricular volume and left atrial area will be recorded with cardiac MRI in all non-randomised participants and compared to baseline left ventricular mass, left ventricular volume and left atrial area to define the specificity of the hs-cTnI assay for identifying low-risk participants who do not develop left ventricular systolic dysfunction. The aim is to demonstrate zero left ventricular mass, left ventricular volume and left atrial area change within the low risk non-randomised group. The specificity of the cTnI assay for left ventricular dysfunction in non-randomised participants will be assessed by calculating the mean of the within-person changes in LVM/LVV/LAA between participants' pre and post-anthracycline MRI scans, plus its 95% confidence interval. There will be no formal testing of equivalence.

5.4.3.4. Exploratory comparison of high-risk to low-risk patients for LVM/LVV/LAA

Population = All recruited patients.

As an exploratory comparison, we will present the mean of the within-person changes between participants' pre and post-treatment LVM LVV and LAA values, plus their 95% confidence intervals, for the (high risk) group randomised to standard care, and for the (low risk) non-randomised group. We will calculate p-values using linear regression, adjusting as specified in Overall Statistical principles.

5.4.4 Hs-cTnI concentrations

Where values are given as '<x ng/L' we will assume that they are equal to x/2 ng/L.

We will use the value taken prior to commencing the first chemotherapy cycle as the baseline value (cycle 1).

We will use the value taken 2 months after the final cycle as the follow up value. If it is missing, we will use the value taken closest in time prior to this.

5.4.4.1 Descriptive statistics
Population = All recruited patients.

We will tabulate baseline values [continuous], and all available follow up values [continuous], within-person change [continuous]; split by non-randomised/randomised, and by allocated intervention within the randomised group.

5.4.4.2. Efficacy analysis - Hs-cTnI
Population = Intention-to-treat.

We will analyse change between baseline and follow up cTnI values.

Using the ITT population, if relevant distributional assumptions hold, then the relationship between the allocated intervention and the outcome will be analysed using linear regression. The results will be expressed as the difference in means with the corresponding 95% confidence intervals and p-value. The analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

5.4.4.3. Exploratory comparison of high-risk to low-risk patients - Hs-cTnI
Population = All recruited patients.

As an exploratory comparison, we will present the mean of the within-person changes between participants' pre and post-treatment values, plus its 95% confidence interval, for the (high risk) group randomised to standard care, and for the (low risk) non-randomised group. We will calculate p-values using linear regression, adjusting as in Overall Statistical Principles.

5.4.4.3.1 Area under the curve (AUC)
Population = All recruited patients.

For each participant, we will calculate the area under the curve of all study Hs-cTnI measurements taken between baseline and the final cycle of chemotherapy, using the trapezium rule. We will remove participants from the analysis if they have insufficient data – for inclusion, a participant must have a baseline value, and must have 4 or more values in total. If the distribution of these across participants is non-Normal, we will use a suitable transformation (for instance by taking the natural logarithm). We will present a summary of these values, separately for those undergoing 3, 4 or 6 cycles of chemotherapy; for the non-randomised group and the group randomised to standard care. We will calculate p-values, comparing between the non-randomised group and the group randomised to standard care, separately for those undergoing 3, 4 or 6 cycles of chemotherapy. We will calculate these using t-tests.

5.4.4.4. Anthracycline cardiotoxicity – hs-cTnI - chronic myocardial injury
Population = All recruited patients.

Chronic myocardial injury defined as persistent elevations of hs-cTnI above the gender-specific 99th centile at 2 months follow up. If the 2-month follow up sample is not available then hs-cTnI elevation above this threshold at any point beyond this will be counted.
There will be no formal statistical testing. We will tabulate the number of patients with and without the above outcome, split by non-randomised/randomised, and by allocated intervention within the randomised group.

Note: Gender specific thresholds (99% upper reference limit) for the Abbott ARCHITECHT assay are <16 ng/L (female) and < 34 ng/L (male)

5.4.4.5. Anthracycline cardiotoxicity – hs-cTnI - risk of severe and early on-treatment cardiotoxicity
Population = All recruited patients.

Any hs-cTnI measurement >80 ng/L during or after treatment. This concentration threshold measured with a contemporary assay has been used previously to define patients at risk of severe and early on-treatment cardiotoxicity.
There will be no formal statistical testing. We will tabulate the number of patients with and without the above outcome, split by non-randomised/randomised, and by allocated intervention within the randomised group.

5.4.5 Clinical outcomes – death, cardiovascular death and heart failure
5.4.5.1 Descriptive statistics
Population = All recruited patients.

We will tabulate whether patients died (all cause), died (cardiovascular) or had heart failure (as 3 separate outcomes). These will be split by randomised/non-randomised and by allocated intervention within the randomised group.

5.4.5.2. Efficacy analysis – death, cardiovascular death and heart failure
Population = Intention-to-treat.

Using the ITT population, for each of these outcomes (death, cardiovascular death and heart failure), we will produce Kaplan-Meier plots of time between randomisation and outcome, split by allocated intervention. Participants will be censored at date of last follow-up or date of non-outcome death. Assuming assumptions hold, we will perform a Cox regression of these data, adjusted as described earlier, and present a Hazard Ratio and 95% confidence interval. An unadjusted analysis will also be performed.

5.4.6 Clinical outcomes – Heart rate and blood pressure
We will use the value taken prior to the first chemotherapy cycle (cycle 1) as the baseline value.

For each outcome, we will use the value taken 2 months after the final cycle as the follow-up value. If it is missing, we will use the value taken closest in time prior to this.

5.4.6.1 Descriptive statistics – Heart rate and blood pressure
Population = All recruited patients.

We will tabulate baseline values [continuous], follow up values [continuous], within-person change [continuous]; split by non-randomised/randomised, and by allocated intervention within the randomised group.

We will also tabulate binary variables defined as: Hypotension: Systolic BP < 90 mmHg, and Bradycardia: Heart Rate < 50 bpm

5.4.6.2. Safety analysis – Heart rate and blood pressure
Population = Intention to treat.

Outcomes of hypotension and bradycardia at follow up
Using the ITT population, the relationship between the allocated intervention and each outcome will be analysed using logistic regression. The results will be expressed as odds ratios with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

5.4.7 Other Safety outcomes

In section 5.4.7, we will consider the following binary outcomes, indicating if the event occurred at any point after consent (we will only count first occurrence):

- Hyperkalaemia (K+ ≥ 5.0 mmol/L)
- Worsening renal function: decrease in eGFR of > 25% from baseline or an increase in creatinine of > 30% from baseline. (For eGFR, any value that is in the database as '>60' will be assumed to be 60 ml/min/1.73m2.)
- Acute kidney injury: An eGFR drop to <45 ml/min/1.73m2
- Fatigue grade ≥2 by CTCAE classification
- New diagnosis of atrial fibrillation

5.4.7.1. Safety analysis - Other Safety outcomes

Population = Intention to treat.

Using the ITT population, the relationship between the allocated intervention and each outcome will be analysed using logistic regression. The results will be expressed as odds ratios with the corresponding 95% confidence intervals and p-value. The analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

5.5 Adverse events

These analyses will use the safety population.

No formal significance testing will be performed.

Summary table of adverse events, by intervention group and overall. Number of events and number of patients who had an event, showing all adverse events, serious adverse events, and non-serious adverse events. Table to include related/not related, and any categorisation provided by the Chief Investigator.

6. Validation and QC

The following will be done by a second statistician:

1. Separate programming and checking of primary outcome results and conclusions.
2. The statistical report will be read and sense-checked, and compared to the list of analyses in this SAP.

7. Data sharing

A file, or set of files, containing the final analysis data will be prepared as part of the final analysis. Within the University of Edinburgh environment, under certain safeguards, these de-identified datasets can be shared. If a fully anonymised version is required for external sharing, further discussion is needed.

8. References

1. SAS® Institute Inc. SAS for Windows. SAS Institute Inc.: Cary, NC, U.S.A

Cardiac CARE SAP v2.0 30JUN2022 clean

Final Audit Report 2022-07-05

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